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**Patent- und Rechtsanwälte**

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(54) **ORAL PHARMACEUTICAL PREPARATIONS DECREASED IN BITTERNESS BY MASKING**

(57) Oral drug compositions or oral medicines wherein the unpleasant tastes inherent in drugs are masked, specifically, granules, powders and syrups decreased in unpleasant tastes by masking and each containing a basic drug tasting unpleasant and an anionic high-molecular substance such as carrageenan.

**EP 0 974 366 A1**

**Description**

## Field of the Invention

- 5 **[0001]** The present invention relates to an oral administration composition or an oral medicine which can prevent an unpleasant taste.

## Prior Art

- 10 **[0002]** For masking a medicine having an unpleasant taste, a lot of techniques have been developed. For example, there is known a method for coating a granulated agent with a water-soluble film (JP-A 4-282312), and a method for obtaining a powder and the like by melting a waxy substance having a melting point in the range of 40 to 100°C wherein a medicine having an unpleasant taste is allowed to be dispersed and then solidified (JP-A 7-267850). On the other hand, for liquids, in order to improve the feeling of taking medicine, there is known a method to use liquids on oral  
15 administration such as syrups, which is widely used as a dosage form suitable for infants, aged people, etc. Although syrup is a dosage form with a sweet taste, when a melted medicine has an unpleasant taste, it is difficult to administer it, because a mere sweet taste cannot prevent an unpleasant taste, and in addition, compliance of a patient is lowered. Moreover, in JP-A 4-346937, as a method for reducing a bitter taste, there has been disclosed a method for reducing a bitter taste which comprises the step of adding a gelling agent selected from agar, gelatin or  $\kappa$ -carrageenan, and a sea-  
20 soning agent to a substance having a bitter taste, so that a jelly state for seasoning is obtained. This method reduces a contact of a bitter taste substance with a tongue by making a jelly state, and a partly melted bitter taste substance masks a bitter taste by the use a seasoning agent.

- [0003]** With a view to masking a medicine having an unpleasant taste, a lot of techniques have been examined as described above, but they have a complicated manufacturing process, an inadequate effect and a problem in quality.  
25 Thus, they have not yet been satisfactory, so that a further technique is required.

## Disclosure of the Invention

- [0004]** The present invention is directed to an oral medicine composition or an oral medicine preventing an unpleasant  
30 taste, which comprises a basic medicine having the unpleasant taste and an anionic polymer, or a method for preventing the same.

**[0005]** A basic substance referred to in the present invention means that its free form shows basicity, and in case of the formation of a salt form, it is not necessarily basic.

- [0006]** In the present invention, a basic medicine having an unpleasant taste should not be limited, therefore, among  
35 orally administrated medicines such as an antibiotic substance, an antimentia medicine, an antiplatelet medicine, an antidepressive medicine, a medicine for improving metabolism of a brain circulation, or an antiallergic medicine, any basic medicine may be used so long as it is one having an unpleasant taste such as a bitter taste, stimulation etc. Embodied examples of the basic substance include ticlopidine hydrochloride, maprotiline hydrochloride, iphenprodil ter-  
40 trate, berberine hydrochloride, digitoxin, sulpyrine, azelastine hydrochloride, etilefrine hydrochloride, diltiazem hydrochloride, propranolol hydrochloride, chloramphenicol, aminophylline, erythromycin, phenobarbital, calcium pantothenic acid, indeloxazine hydrochloride, aminoguanidine hydrochloride, donepezil hydrochloride, (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7-((z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide)-3-N,N-dimethylcarbamoyloxymethyl-8-  
45 oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt, cefcapene hydrochloride and the like. Among these compounds, for donepezil hydrochloride and (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7-((z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide)-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-  
en-2-carboxylate hydrochloride salt, an especially excellent effect is exerted. Donepezil hydrochloride is chemically named 1-benzyl-4-(5,6-dimethoxyindanon-2-yl)methylpiperidine hydrochloride salt, which is therapeutic medicine for Alzheimer disease of a slight to a medium degree, and its aqueous solution has a sharp bitterness and a numbness in  
50 a mouth. In addition, (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7-((z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide)-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride is an effective antibiotics on oral administration, however, it has a strong bitter taste.

- [0007]** Although an anionic polymer referred to in the present invention should not especially be limited, an acidic polysaccharide is preferable, and typical examples include carrageenan, chondroitin sulfate, dextran sulfate, alginic acid, gerun gum, xanthan gum and a salt form thereof. With regard to carrageenan, some kinds such as  $\iota$ ,  $\kappa$ ,  $\lambda$  and the  
55 like are known, and any kind can be used, and especially, for liquids or jellies,  $\kappa$ -carrageenan and  $\lambda$ -carrageenan are preferable, and dextran sulfate is also preferable.

**[0008]** For solids, especially  $\kappa$ -carrageenan, chondroitin sodium sulfate and sodium alginate are preferable.

**[0009]** Carrageenan on the market can be used, and it is obtainable from FMC Corporation : USA, Systems Bio Indus-

tries Co., Ltd. etc.

**[0010]** An oral medicine regarding the present invention means a dosage form which can be orally administrated as solids, liquids or jellies. Typical examples of the solids include granules, fine granules, powders, tablets, pills etc., and typical examples of the liquids include syrups, elixirs, emulsions, suspensions and the like, and especially, a case of granules, fine granules, powders, syrups and jellies are preferable.

**[0011]** These dosage forms are described in the Japanese Pharmacopoeia except for jellies.

**[0012]** A method for administration of an oral medicine related to the present invention should not be especially limited, and according to a property of a medicine, the oral medicine can be orally administrated one to several times per day before, after or between meals.

**[0013]** Since the amount of a medicine in solids is different according to a property of a medicine, it is not generally spoken, but the amount of the medicine at one administration is usually in the range of 0.1 to 1000 mg.

**[0014]** The concentration of a medicine in oral liquids which prevents an unpleasant taste is usually in the range of 0.1 to 500 mg/ml, preferably in the range of 0.5 to 100 mg/ml. When a medicine is donepezil hydrochloride, the concentration is preferably in the range of 0.5 to 5 mg/ml.

**[0015]** In the present invention, the proportion of an anionic polymer to a basic substance is usually in the range of 0.1 to 20 parts by weight, preferably 0.5 to 10 parts by weight with respect to 1 part by weight of a basic substance.

**[0016]** In the case that the oral medicine regarding the present invention is the solids, the medicine and the anionic polymer are homogeneously mixed to obtain an effect of preventing an unpleasant taste. Furthermore, the medicine and fillers and the like are mixed, and separately, an anionic polymer is dissolved in a solvent such as water, mixed with another binding agent, if necessary, and then gradually added to the medicine to be granulated, as a result, an effect of preventing an unpleasant taste is also obtainable. Depending upon a kind of a medicine, some medicines have greater effect preventing an unpleasant taste by being granulated.

**[0017]** A method for manufacturing an oral medicine preventing an unpleasant taste related to the present invention should not be especially limited, and the medicine can be manufactured by a method which is usually used. For example, for granules, fillers such as lactose, mannitol, starch and crystalline cellulose etc., disintegrants and the like such as carboxymethylcellulose etc. are further mixed into a medicine and  $\kappa$ -carrageenan, with adding a solution wherein a binding agent such as hydroxypropylcellulose, the granules can be manufactured by the use of a granulator which is usually used. And in addition, a method for manufacturing an oral liquid medicine should not be especially limited. For example, a basic medicine and an anionic polymer are solved in water to manufacture the oral liquids. Furthermore, a sweetening agent such as cane sugar, xylitol, mannitol, glucose, aspartame and saccharin, and a taste-reforming agent such as vanilla essence and apple odor can be added to it. Since the oral medicine related to the present invention prevents an unpleasant taste, characteristic of the medicine, such as a bitter taste, numbness and contraction, it is easily administrated and compliance of a patient improves. Especially, it is effective on infants and aged people. A mechanism that the oral medicine related to the present invention prevents an unpleasant taste is considered as follows. That is to say, it is considered that when a basic substance having an unpleasant taste brings about an interaction with an acidic polysaccharide to be dissolved in saliva, or through decrease of free forms in a solution, a bonding rate of the basic substance to a receptor of a tongue is decreased, and in addition, appearance of numbness is also decreased.

#### Experimental Example

##### Test 1

**[0018]** 2 mg/ml of an aqueous donepezil hydrochloride solution was prepared. After 50 mg of  $\kappa$ -carrageenan, chondroitin sulfate or dextran sulfate was dissolved in 5 ml of the aqueous solution. Two examinees (which were represented by A and B in Table) hold the whole amount of the solution in their mouths, and then evaluated the degree of a bitter taste and numbness in accordance with five grades. The results are shown in Table 1.

**[0019]** As is apparent from Table 1, a bitter taste of donepezil hydrochloride can be remarkably controlled by the addition of  $\lambda$ -carrageenan and the like.

##### Test 2

**[0020]** By the use of ticlopidine hydrochloride (20 mg/ml), maprotiline hydrochloride (5 mg/ml) and iphenprodil tartaric acid (4 mg/ml), an effect of carrageenan preventing a bitter taste and numbness was examined. A method of examination and a standard of evaluation were based on Test 1. The results are shown in Table 2.

**[0021]** As is apparent from Table 2, a bitter taste and numbness of each medicine can be remarkably controlled by the addition of carrageenan. Especially, a taste of ticlopidine hydrochloride is extremely bitter and stimulative, but it proves the extremely excellent effect of the present invention that the bitter taste and numbness can be remarkably controlled by addition of carrageenan.

Test 3

**[0022]** Sodium alginate, sodium chondroitin sulfate, κ-carrageenan, ι-carrageenan, mannitol, cornstarch, copolyvidon and the like were blended with (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7-((z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide)-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt (which was shown as a compound A in Table 3) in ratios shown in Table 2, and granules were prepared in accordance with the method of Example 3. The test was carried out by three examinees holding 0.5 g of each granule for examination in their mouths, and the judgment was done by an evaluation standard of seven grades shown as follows.

+4: impossible to administrate because of a severe bitterness, +3: very bitter, +2: bitter, +1: a little bitter, 0: neither taste, -1: feeling no bitterness, -2: rather delicious

The results are shown in Table 3.

**[0023]** It is apparent from Table 3 that the granules combined with the anionic polymer related to the present invention remarkably controls a bitter taste.

Test 4

**[0024]** According to the treatment shown in Table 4, ticlopidine hydrochloride, κ-carrageenan, cornstarch, mannitol and hydroxypropylcellulose (which was represented by HPC-L in Table 4) were sufficiently mixed and water was then added, and they were granulated to obtain granules. Two examinees held 0.5 g of this granules in their mouths, and the judgment was done. The evaluation standard was based on Example 1. The result was shown in Table 4.

**[0025]** It is apparent from Table 4 that the present applied invention can prevent an extremely unpleasant taste of ticlopidine even in the solid state.

**[0026]** From the tests shown above, the remarkable effect of the present applied invention is evident.

Examples

**[0027]** Next, the present invention will be described in more detail in accordance with examples, but the scope of the present invention should not be limited by these examples.

Example 1

**[0028]** 100 mg of donepezil hydrochloride, 300 mg of sodium saccharin and 14 g of povidone were dissolved in 50 g of purified water., and separately, 700 mg of κ-carrageenan was added to 50 g of purified water, and it was were heated at 80°C to be dissolved. After it was cooled down, both solutions were mixed, and 300 mg of methylparabene and 20 mg of propylparabene were dissolved in a small quantity of propyleneglycol to be added to the above mixture, so that syrups were manufactured.

Example 2

**[0029]** 40 g of xylitol was added to 50 g of purified water, and they were heated at 80°C to be dissolved. And separately, 200 mg of donepezil hydrochloride was dissolved in 50 ml of purified water, and wherein 0.56 g of κ-carrageenan, 1.0 g of λ-carrageenan, 0.15 g of locust bean gum, 0.22 g of gerun gum, 0.15 g of xanthan gum, 0.19 g of sodium citrate, 0.19 g of calcium lactate, 0.94 g of lactose and 40 g of powdered hydrogenated maltose starch syrup were added, and in addition, the previously prepared xylitol-containing purified water was added therein, and they were stirred at 90°C. After the mixture was cooled down to 80°C, 0.6 g of citric acid was mixed therein, to which purified water was added, so that the total weight was 200 g. It was pipetted into vessels in a portion of 10 g and then cooled down to manufacture jellies.

Example 3

**[0030]** 15 g of (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7-((z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide)-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt, 15 g of κ-carrageenan, 30 g of cornstarch and 40 g of mannitol were mixed by the use of the rolling granuator, and about 20 ml of water was slowly added therein and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Example 4

[0031] 15 g of the drug substance medicine used in Example 3, 15 g of sodium condroitin sulfate and 70 g of mannitol were mixed by the use of the granulator, and about 20 ml of water was slowly added therein and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Example 5

[0032] 15 g of the drug substance used in Example 3, 15 g of carrageenan (mixture of ι-carrageenan and κ-carrageenan), 15 g of copolyvidon and 55 g of mannitol were mixed by the use of the granulator, and about 15 ml of water was slowly added therein and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Example 6

[0033] 58 g of the drug substance used in Example 3, 58 g of κ-carrageenan, 120 g of cornstarch, 130 g of mannitol and 16 g of aerosil were mixed, whereon 8 g of sodium alginate dissolved in 392 ml of water and a slight amount of Red-102 pigment were sprayed by the use of the fluidized bed granulator, and then they were dried. Next, 2 g of strawberry essence was sprayed thereon and they were dried, wherein 8 g of aspartame was mixed, so that fine granules were manufactured.

Example 7

[0034] 15 g of the drug subetnace used in Example 3, 14.5 g of κ-carrageenan, 30 g of cornstarch and 40 g of mannitol were mixed, whereon 0.5 g of λ-carrageenan dissolved in 25 ml of water was sprayed by the use of the fluidized bed granulator, so that fine granules were manufactured.

Example 8

[0035] 10 g of cefcapene pivoxil hydrochloride, 10 g of κ-carrageenan, 30 g of cornstarch, 48 g of mannitol and 2 g of aspartame were mixed by the use of a rolling granulator, and 20 ml of water was slowly added thereto and wet mass was manufactured, and then dried through a screen with 32 meshes, so that granules were manufactured.

Table 1

Standard of Evaluation					
Bitterness	No Feeling	Dim Feeling	Slightly bitter	Bitter	Very bitter
Numbness	No Feeling	Dim Feeling	Slightly numb	Numb	Very numb
	-	±	+	++	+++
Results					
Sample/Examinee		A		B	
		Bitterness	Numbness	Bitterness	Numbness
Donepezil hydrochloride		+++	+++	+++	+++
Donepezil hydrochloride + κ-Carrageenan		+	±	+	+
Donepezil hydrochloride + Chondroitin sulfate		++	++	+++	++
Donepezil hydrochloride + Dextran sulfate		+	±	+	+

Table 2

Sample/Examinee	A		B	
	Bitterness	Numbness	Bitterness	Numbness
Ticlopidine sulfate	+++	+++	+++	+++
Ticlopidine sulfate				
+ $\kappa$ -Carrageenan (1 mg/ml) + $\lambda$ -Carrageenan (1 mg/ml)	$\pm$	++	$\pm$	++
Ticlopidine sulfate + $\kappa$ -Carrageenan (2 mg/ml)	-	+	-	$\pm$
Maprotiline hydrochloride	++	+	+	+
Maprotiline hydrochloride + $\kappa$ -Carrageenan (2 mg/ml)				
Ipheprodil tartaric acid	+	-	++	-
Ipheprodil tartaric acid + $\kappa$ -Carrageenan (2 mg/ml)	$\pm$	-	-	-

Table 3

Composition	Prescription(%)	Evaluator A	Evaluator B	Evaluator C
Compound A	15	+4	+3	+4
Mannitol	85			
Compound A	15	+1	0 to +2	+1
Sodium alginate	15		Note 1	
Mannitol	70			
Compound A	15	0	0	0
Sodium chondroitin sulfate	15			
Mannitol	70			
Compound A	15	0	0	0
$\kappa$ -Carrageenan	15			
Cornstarch	30			
Mannitol	40			
Compound A	15	-1	0 to +1	0
$\kappa$ & $\lambda$ -Carrageenan	15		Note 1	
Copolyvidon	15			
Mannitol	55			
Compound A	15	0	-1	0
$\kappa$ -Carrageenan	14.5			
$\lambda$ -Carrageenan	0.5			
(solvent was added)				
Cornstarch	30			
Mannitol	40			

Table 3 (continued)

Composition	Prescription(%)	Evaluator A	Evaluator B	Evaluator C
Compound A	14.5	-2	-2	-2
κ-Carrageenan	14.5			
sodium alginate	2			
(solvent was added)				
Cornstarch				
Mannitol	30			
Aerosil	32.5			
Strawberry essence	4			
Red No. 102	0.5			
Aspartame	Trace			
	2			
Note 1: When it was administered with water, the bitterness was felt afterward.				

Table 4

			Control	Prescription 1	Prescription 2	prescription 3
Prescription	Ticlopidine		100	100	100	100
	κ-Carrageenan		0	100	200	300
	Mannitol		670	570	470	370
	Cornstarch		200	200	200	200
	HPC-L		30	30	30	30
	Total		1000	1000	1000	1000
Results	A	Bitterness	+	±	-	-
		Numbness	+++	+++	+	±
	B	Bitterness	+	+	-	-
		Numbness	+++	+++	±	-
mg/g of a granule						

### Claims

1. An oral medicine composition preventing an unpleasant taste which comprises a basic medicine having the unpleasant taste and an anionic polymer.
2. The medicine composition according to Claim 1 wherein the anionic polymer is at least one selected from the group consisting of carrageenan, chondroitin sulfate, dextran sulfate, alginic acid, gerun gum, xanthan gum and salts thereof.
3. The medicine composition according to Claim 1 wherein the basic medicine having the unpleasant taste is an anti-biotic, an antidementia medicine, an antiplatelet medicine, an antidepressive medicine, a medicine for improving

metabolism of a brain circulation, or an antiallergic medicine.

4. The medicine composition according to Claim 1 wherein the basic medicine having the unpleasant taste is donepezil hydrochloride.
- 5 5. The medicine composition according to Claim 1 wherein the basic medicine having the unpleasant taste is (RS)-1-(isopropoxycarbonyloxy)ethyl(+)-(6R,7R)-7-((z)-2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamide)-3-N,N-dimethylcarbamoyloxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octo-2-en-2-carboxylate hydrochloride salt.
- 10 6. The medicine composition according to Claim 1 wherein the anionic polymer is contained in an amount of 0.1 to 20 parts by weight with respect to 1 part by weight of the basic substance having the unpleasant taste.
7. The composition according to Claim 1 wherein the medicine is granules, fine granules, powders, liquids, syrups or jellies.
- 15 8. A method for preventing an unpleasant taste which comprises the step of blending an anionic polymer with a basic medicine having an unpleasant taste.

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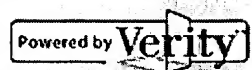
## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01360

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int.Cl. <sup>6</sup> A61K47/36  According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int.Cl. <sup>6</sup> A61K47/36  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 4-346937, A (Kibun Food Chemifa Co., Ltd.), December 2, 1992 (02. 12. 92) (Family: none)	1
A	JP, 4-346937, A (Kibun Food Chemifa Co., Ltd.), December 2, 1992 (02. 12. 92) (Family: none)	2-8
A	JP, 54-76818, A (Ejito Jiojiserubajesechi Jaru), June 19, 1979 (19. 06. 79) (Family: none)	1-8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search May 19, 1998 (19. 05. 98)		Date of mailing of the international search report May 26, 1998 (26. 05. 98)
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